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EFFECT OF INCREASING DOSES OF IONIZING RADIATION ON LIVER ENZYMES INVOLVED IN FATTY ACID SYNTHESIS

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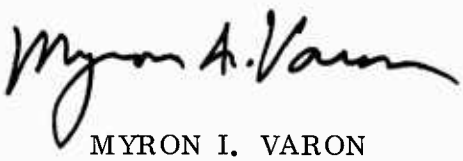

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FOREWORD
(Nontechnical summary)

Cellular membranes contain large amounts of lipids which are made mainly of long chain fatty acids. Acetyl coenzyme A carboxylase and fatty acid synthetase are the key enzymes responsible for the synthesis of these fatty acids from two-carbon units. Since radiation can affect membranes, it was logical to investigate its effect on these two key enzymes. It was found in this study that the activities of both enzymes were affected by radiation. When increasing doses of radiation were given to the animals (rats) the activities of both enzymes were increased until they reached maximal values. Then, as the radiation dose was further increased, the activities of the enzymes declined. This response of activity was observed whether the animals were exposed to x rays or to mixed neutron-gamma radiation. However, much lower radiation doses were necessary to achieve maximal values using the mixed neutron-gamma radiation than were needed with x rays. It was also observed that the effect of mixed neutron-gamma radiation on the activity of acetyl CoA carboxylase was more pronounced than that with x rays and that this activity decreased. In contrast, fatty acid synthetase showed a greater sensitivity in activity (increase) in animals irradiated with x rays than with mixed neutron-gamma radiation.

ABSTRACT

The effect of increasing doses of x rays and of mixed neutron-gamma radiation on the fatty acid synthesizing liver enzyme system in rats has been investigated. It was found that the activity of this enzyme system first increased with radiation dose and then decreased in rats exposed to either x rays or mixed neutron-gamma radiation. Acetyl CoA carboxylase activity was found to be more sensitive to mixed neutron-gamma radiation (decreased) than to x rays, whereas fatty acid synthetase appeared to be more sensitive to x rays (increased) than to mixed neutron-gamma radiation.

I. INTRODUCTION

The effect of x rays on the fatty acid synthesizing liver enzyme system has been studied by several investigators, and it has been reported in both rats and mice exposed to x radiation that the incorporation of ^{14}C acetate into fatty acids was increased.[6,9,11,13,14] The specific activities of enzymes involved in the biosynthesis of fatty acids were measured in particle-free liver homogenates obtained from mice exposed to 690 R of x rays and sacrificed over a period of 14 days postirradiation.[1] The obtained results indicated that acetyl CoA carboxylase was the enzyme which was mainly influenced by irradiation of the animal. Results of previous experiments concerned with the in vivo effects of ionizing radiations on the fatty acid synthesizing liver enzyme system[4] indicated that when rats were exposed to 1200 R of x rays or of ^{60}Co gamma rays the activity of the enzyme system was greatly enhanced. This increase was found to reach a more than twelvefold level in animals sacrificed 24 hours after exposure and it was somewhat lower in rats that received the same dose of ^{60}Co gamma rays. In contrast, preliminary results obtained in our laboratory* showed that when the animals were exposed to the same dose of 14 MeV neutron radiation, the activity of the same enzyme system was inhibited by approximately 15 to 20 percent.

The objective of this study was to investigate the cause(s) of the observed differences in activity changes between rats exposed to x rays and rats that received neutron radiation. To investigate these differences, a series of experiments were performed in which groups of rats were exposed to increasing doses of x rays or of mixed neutron-gamma radiation (neutron to gamma ratio of 7 to 1).

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* Unpublished data

II. PROCEDURES AND METHODS

Four hundred and eighty female Sprague-Dawley rats approximately 4 to 5 weeks old and weighing 100 to 120 grams were divided into two groups of 240 each. The first group was utilized to determine the effect of increasing doses of ionizing radiation on the fatty acid synthesizing liver enzyme system. The second group was used to study the effect of radiation on the enzymes acetyl CoA carboxylase and fatty acid synthetase which are involved in the biosynthesis of fatty acids. The animals were kept in a temperature-controlled room at 22°C and were housed in cages (two per cage). They were fed a high carbohydrate fat-free diet for at least 7 days prior to irradiation. Each rat received approximately 12 - 13 grams of food (laboratory pellets) per day. The entire ration was given at one time and the animals were trained to consume it within 1 to 1-1/2 hours. The animals were exposed to radiation approximately 2 hours after they had consumed their food. No food was given to the animals following irradiation. Sham irradiated controls were also deprived of food over a period of time corresponding to that of the irradiated rats. All animals had free access to water.

Sixty rats were used for each of four experiments in the study of the effect of increasing doses of ionizing radiation on the fatty acid synthesizing liver enzyme system. The animals utilized in each experiment were divided into three groups as follows: 30 rats were x irradiated, 24 rats were exposed to mixed neutron-gamma radiation, and 6 rats were sham irradiated and used as controls.

The study of the effects of ionizing radiation on the activity of the enzymes involved in fatty acid synthesis employed 240 rats utilizing 48 animals in each of five experiments. These 48 animals were divided into three groups as follows: 24 rats

were exposed to x rays, 18 rats were exposed to mixed neutron-gamma radiation, and 6 rats were sham irradiated and used as controls. During exposure the animals were individually housed in Lucite boxes which were so arranged that each rat received an equal unilateral exposure. The tissue kerma rate, free-in-air, at the midline of the animal was 65.5 rads/minute. The physical characteristics of the radiation sources were as follows:

X rays. A 250 kVp x-ray generator with inherent filtration of 1.2 mm beryllium and added filtration of 0.95 mm copper was used. The distance from the source to the midline of each rat was 59 cm.

Mixed neutron-gamma radiation. The AFRRI-TRIGA reactor was used as the radiation source. The rats, individually housed in Lucite boxes, were placed in the exposure room so that the kerma to each rat did not vary by more than 4-5 percent. The distance from the center line of the reactor to the midline of each rat was 100 cm. To increase the neutron to gamma ray ratio, the core of the reactor was shielded with a wall 4 inches thick of lead bricks. A ratio of neutrons to gamma rays of 7 to 1 was thus obtained. This was measured using a paired chamber technique, i.e., a 50 cm^3 tissue-equivalent chamber filled with tissue-equivalent gas and a 50 cm^3 graphite chamber filled with CO_2. Sulfur tablets were used for neutron monitoring on all Lucite boxes.

Following removal from the exposure room, three animals from each experimental group, as well as from the sham irradiated controls, were sacrificed by decapitation at 3 or 24 hours postirradiation. The livers were immediately excised, chilled in an ice-cold isotonic solution of sodium chloride, and homogenized in a

medium containing phosphate buffer, sucrose, nicotinamide and magnesium chloride. The exact composition of the medium, conditions of homogenization, and subsequent treatment are described elsewhere.[5] The substrate in this series of experiments was 1-^{14}C-acetate. The amount of radioactivity found in the isolated fatty acids, which is a measure of the activity of the fatty acid synthesizing liver enzyme system, was calculated as counts per minute per milligram of fatty acids. The data obtained from the control animals were normalized at 100 for comparison with the other values.

Acetyl CoA carboxylase activity was determined according to the method of Greenspan and Lowenstein.[8] The assay system of Butterworth et al.[3] with minor modifications was used to determine fatty acid synthetase activity. The results for both enzymes were expressed as counts per minute per milligram of protein. Protein determinations were carried out according to the method of Lowry et al.[12]

III. RESULTS

The results shown in Figure 1 were obtained when rats were exposed to increasing doses of x rays or of mixed neutron-gamma radiation. It can be seen that in x irradiated rats sacrificed 3 hours after exposure the activity of the fatty acid synthesizing liver enzyme system first increased with radiation dose, reaching maximal values at doses between 1200 and 2000 rads, and then declined. In animals sacrificed 24 hours after exposure, the pattern of activity change was basically the same, though more pronounced. A greater than twelvefold increase in enzymic activity occurred at radiation doses between 1200 and 2000 rads of x rays. A similar increase in enzymic activity was observed in rats exposed to mixed neutron-gamma radiation and sacrificed 3 hours after exposure. However, maximal values of enzymic activity were

observed in the range between 400 and 800 rads. As the radiation dose increased above these levels, the enzymic activity declined. In animals sacrificed 24 hours after exposure to mixed neutron-gamma radiation, the pattern of activity change was the same although the increase at doses between 400 and 800 rads was much smaller.

The effect of ionizing radiation on the activity of acetyl CoA carboxylase is shown in Figure 2. It can be seen that no significant changes occurred in the activity of this enzyme when the animals were exposed to x rays at doses of up to 4000 rads and sacrificed at 3 or 24 hours after irradiation. In contrast, a pronounced inhibition of activity was observed in animals exposed to mixed neutron-gamma radiation. This inhibition reached a level of approximately 50 percent of the control values in rats which received 2000 rads of radiation.

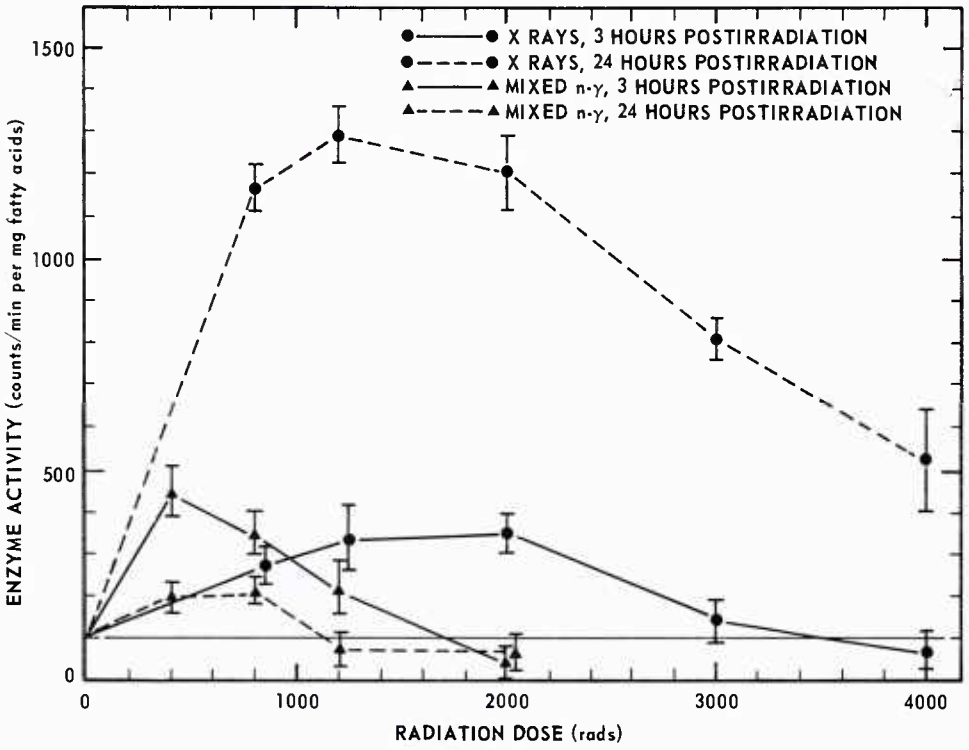

Figure 1. Effect of ionizing radiation on activity of fatty acid synthesizing liver enzyme system

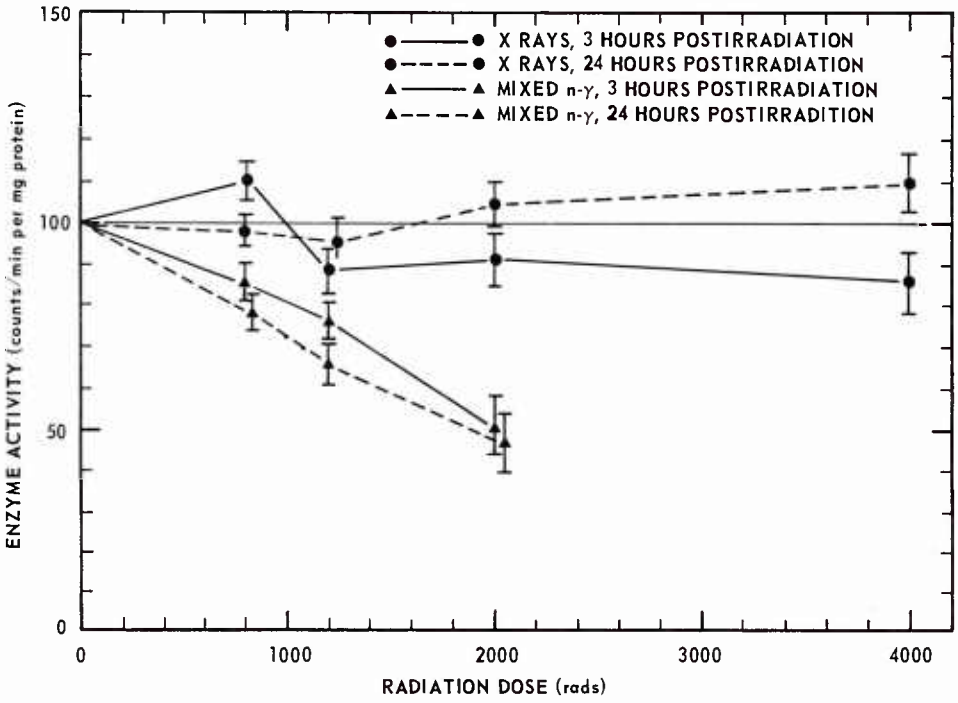

Figure 2. Effect of ionizing radiation on activity of acetyl CoA carboxylase

Figure 3 shows the effects of ionizing radiation on the activity of fatty acid synthetase. It can be seen that exposure of rats to 800 rads of mixed neutron-gamma radiation caused an approximately 75 percent increase in the activity of this enzyme in animals sacrificed 3 hours postirradiation. This stimulation was less in rats sacrificed 24 hours after exposure. Then, as radiation doses increased, the activity of this enzyme declined whether the animals were sacrificed at 3 or 24 hours postirradiation. The effect of x rays on the activity of fatty acid synthetase was more pronounced. In animals sacrificed 3 hours after exposure a more than twofold increase in activity was observed at doses between 800 and 2000 rads. At higher radiation doses the activity of this enzyme declined. In animals sacrificed 24 hours after x irradiation, the

enhancement of activity was more pronounced. A more than sixfold stimulation was observed in rats exposed to 800 rads.

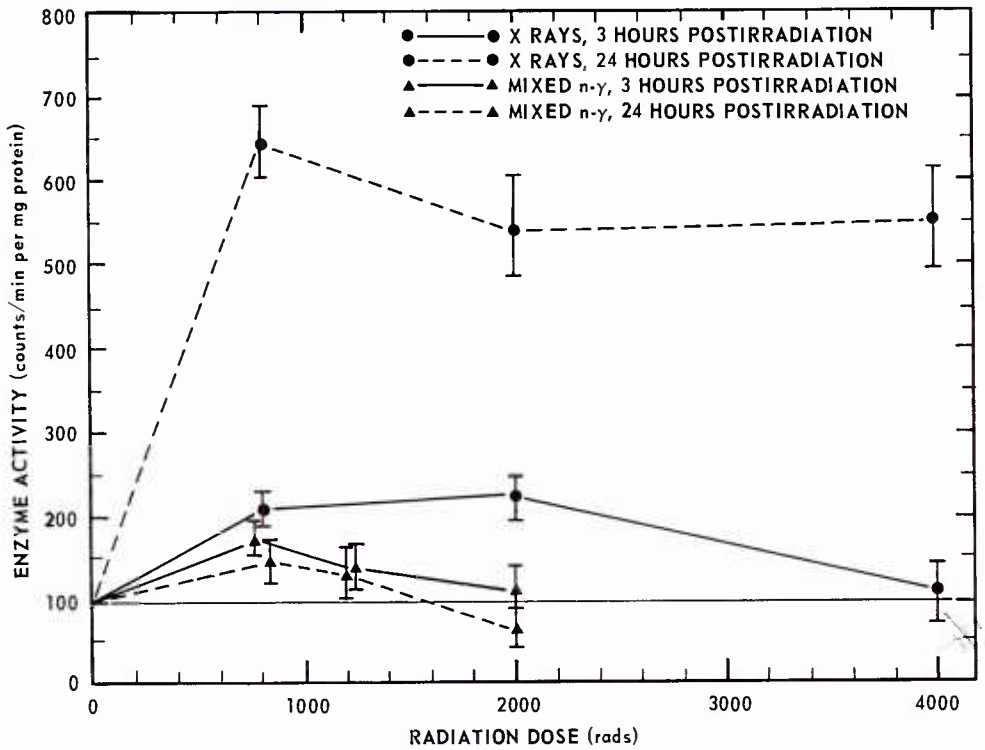

Figure 3. Effect of ionizing radiation on activity of fatty acid synthetase

IV. DISCUSSION

Earlier observations in this laboratory indicated that the activity of the fatty acid synthesizing liver enzyme system was stimulated when rats were exposed to 1200 R of whole-body x irradiation, whereas similar doses of 14 MeV neutron radiation* resulted in inhibition of enzymic activity. Results of the present study show that in rats exposed to increasing doses of x rays, the activity of the same enzyme system increases with dose, reaches maximal values at doses between 1000 and 2000 rads,

* Unpublished data

and then declines. A similar response of enzymic activity change was also observed in animals exposed to mixed neutron-gamma radiation with increased neutron to gamma ratio. However, maximal values were obtained at lower doses, approximately 400 to 800 rads. These differences in response of enzymic activity change between rats exposed to x rays and animals exposed to mixed neutron-gamma radiation could be explained by differences in the relative biologic effectiveness of the two qualities of radiation.

It has been reported[1] that whole-body irradiation of mice with 690 R of x rays affects the activities of enzymes participating in the biosynthesis of fatty acids and it was found that in fed mice a few hours after exposure liver acetyl CoA carboxylase was significantly enhanced and then decreased to values corresponding to fasted control mice within 48 hours. It was also observed by the same authors that the activity of fatty acid synthetase decreased immediately after irradiation without an initial increase.

Activity determinations of acetyl CoA carboxylase in the livers of irradiated and control rats indicate that under our experimental conditions, in fed rats sacrificed 3 hours after exposure to 800 rads of x rays, acetyl CoA carboxylase was enhanced when compared to that of control fed animals. In rats sacrificed 24 hours after exposure, the activity values of this enzyme appeared to be below those for the corresponding unirradiated controls (i.e., rats starved for 24 hours). Although the experimental conditions and the animal species were different in the present study as compared with the above-cited report,[1] it is of interest to note that similar results were obtained. In the present study, higher radiation doses of x rays inhibited the activity of this enzyme

when animals were sacrificed 3 hours after irradiation, whereas in animals sacrificed 24 hours after irradiation acetyl CoA carboxylase activity seemed to be restored or even slightly enhanced. Exposure of rats to mixed neutron-gamma radiation resulted in inhibition of acetyl CoA carboxylase which became more pronounced as the radiation dose increased.

In contrast to the findings of other investigators with mice[1] our results indicate that fatty acid synthetase activity increased by exposure of rats to x rays and that this increase was more pronounced when the animals were sacrificed 24 hours after exposure. It was also found that in rats exposed to mixed neutron-gamma radiation the activity of this enzyme appeared to be enhanced at doses of approximately 800 rads and then declined.

The differences in fatty acid synthetase activity response to x irradiation between our results with rats and of others with mice could probably be due to the use of different species of animals. It has been shown, for instance,[11] that the stimulation of lipogenesis by x irradiation depends on the species of the animal and that it occurs in liver preparations obtained from rats but not from mice.

It is not clear, at present, to what extent synthetase participates in the activity changes observed in this study or whether acetyl CoA carboxylase contributes more to the system than the results indicate. The factors which could play a role in the activity changes observed have not been investigated in this study. It is possible that these changes may be due to net enzyme synthesis or destruction or to other factors such as aggregation or disaggregation of existing enzyme molecules. For example the activation of acetyl CoA carboxylase is accompanied by an increase in its

sedimentation constant[16] and polymerization of its subunits.[15] On the other hand, x ray diffraction studies and electron-density maps have revealed the presence of "cavities" in the active site regions of crystalline enzymes, which presumably contain loosely organized water molecules.[2, 7, 10] Assuming that such structural configurations may be a general characteristic of enzyme molecules, one could hypothesize that, at lower doses at which enzyme systems may be minimally damaged by radiation, in addition to other radiation-induced changes, a contributing factor could be disruption of "orientation" of these water molecules resulting in increased accessibility of the active site to the substrate molecules and perhaps partial extrusion of water from the cavity. However, as radiation dose increases, direct or indirect biochemical damage of the enzyme system would result in the decrease of its activity.

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13. ABSTRACT

The effect of increasing doses of x rays and of mixed neutron-gamma radiation on the fatty acid synthesizing liver enzyme system in rats has been investigated. It was found that the activity of this enzyme system first increased with radiation dose and then decreased in rats exposed to either x rays or mixed neutron-gamma radiation. Acetyl CoA carboxylase activity was found to be more sensitive to mixed neutron-gamma radiation (decreased) than to x rays, whereas fatty acid synthetase appeared to be more sensitive to x rays (increased) than to mixed neutron-gamma radiation.

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